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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	PAPER NUMBER
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,384	RIDDER ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2009*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-39, 42, 43, and 47-49* is/are pending in the application.

4a) Of the above claim(s) *36-38 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,39,42,43,48 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 18, 2009 has been entered.

1. The amendment filed March 18, 2009, is acknowledged and has been entered. Claims 35, 38, and 39 have been amended.

2. Claims 35-39, 42, 43, and 47-49 are pending in the application. Claims 36-38 and 47 has been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species of invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 1, 2008.

3. Claims 35, 39, 42, 43, 48, and 49 are currently under prosecution.

Grounds of Objection and Rejection Withdrawn

4. Unless specifically reiterated below, Applicant's amendment has obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed January 30, 2009.

Grounds of Objection Maintained

Specification

5. The objection to the specification because the use of improperly demarcated trademarks is maintained. Although the use of trademarks is permissible in patent

applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although it appears that Applicant may have made a *bona fide* attempt to resolve this deficiency by appropriately amending the specification, an additional example of an improperly demarcated trademark appearing in the specification is noted, namely EnVision™; see, e.g., the substitute paragraph at page 29, line 4.

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 35, 39, 42, 43, 48, and 49 are rejected under 35 U.S.C. 103(a), as being unpatentable over Martin et al. (*Am. J. Pathol.* 2000 May; **156** (5): 1573-1579).

Claims 35, 39, 42, 43, 48, and 49 are drawn to a kit comprising a first primary antibody that binds to $p16^{INK4a}$ polypeptide, a second primary antibody that binds to Ki67 polypeptide, and a sample of cervical cells expressing $p16^{INK4a}$ and Ki67, which could be used as a positive control.

Martin et al. describes a study in which antibodies that specifically bind to $p16^{INK4a}$ or Ki67 were used; see entire document (e.g., the abstract). Moreover, Martin

et al. describes an experiment in which cells expressing $p16^{INK4a}$ and/or Ki67 were "double labeled" with antibodies that bind to $p16^{INK4a}$ or Ki67, so as to permit simultaneous detection of the antigens; see, e.g., page 1574, column 2.

Martin et al. teaches kits comprising reagents for the detection $p16^{INK4a}$ or Ki67 (see, e.g., page 1574, column 2), but does not expressly teach a kit comprising an antibody that specifically binds to $p16^{INK4a}$ and an antibody that specifically binds to the Ki67/Ki-S5 antigen.

Nonetheless, in light of the disclosure by Martin et al., and in view of teachings, suggestions, or other motivation found in the knowledge generally available to one of ordinary skill in the art at the time the invention was made, it would have been *prima facie* obvious to one of ordinary skill in the art at the time to have manufactured a kit comprising an antibody that specifically binds to $p16^{INK4a}$ and an antibody that specifically binds to the Ki67/Ki-S5 antigen, since, in particular, Martin et al. teaches an dual analysis of the levels of $p16^{INK4a}$ and Ki67in cells using detectably labeled antibodies that specifically bind to $p16^{INK4a}$ or Ki67. Given such disclosure, it follows logically that a kit comprising an antibody that specifically binds to $p16^{INK4a}$ and an antibody that specifically binds to the Ki67/Ki-S5 antigen could be used to detect $p16^{INK4a}$ and the Ki67/Ki-S5 antigen; so therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to do so since such kits had become widely used in such research, having established utility in such expression studies, for example, and providing ease of use and convenience, as well as greater uniformity and control.

In addition, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to include in the kit one or more "positive controls", namely a sample of a $p16^{INK4a}$ polypeptide and/or ki67 polypeptide (or alternatively a cell that expresses one or both of these proteins) to which the antibodies positively bind and which could be used in assays designed to access the presence of $p16^{INK4a}$ and/or Ki67 (or the presence of cells expressing one or both of the proteins) in biological samples. The use of such positive controls was routine and conventional at the time. The inclusion of such a positive control in the kit would greatly ease use of the

kit to detect $p16^{INK4a}$ and Ki67 (or the detection of cells expressing the proteins) in biological samples because it would not have been necessary to develop a positive control, where one has already been provided.

Although Martin et al. does not expressly describe a *cervical* cell, per se, which expresses both $p16^{INK4a}$ and Ki67, which may be used as a positive control, and which could be included in a kit as a positive control, it is submitted that it would have been *prima facie* obvious to utilize any cell, including a cervical cell that expresses $p16^{INK4a}$ and Ki67 as a positive control.

It is important to note that Ki67 is a marker of proliferation, which is ubiquitously expressed throughout the cell cycle[1] by most, if not all cells, including cervical cells. In other words, all cycling cells express Ki67. This is presumably at least one of the reasons that Martin et al. chose Ki67 as a marker, since it is apparent that Martin et al. intended to study the proliferation of cells expressing $p16^{INK4a}$.

Then, as Martin expressly teaches, $p16^{INK4a}$ is a regulator of the cell cycle and thus functions to control the proliferation of cells.

As such, any cell, such as a cervical cell, would be instantly recognized as a cell that could be suitably used as such a positive control, provided that cell is known to express $p16^{INK4a}$ and Ki67.

The expression of $p16^{INK4a}$ by cervical cells had been described[2] and the expression of Ki67 by cervical cells had been described[3]; moreover, the expression of both $p16^{INK4a}$ and Ki67 was a fact well known by the artisan of ordinary skill in the art at the time the application was filed.

Furthermore, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to include in the kit labeled antibodies that specifically bind to $p16^{INK4a}$ or the Ki67/Ki-S5 antigen since such antibodies could be used directed without the need of secondary antibodies and indirect labeling methods. The inclusion of such labeled antibodies in the kit would greatly ease use of the kit to

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[1] See, e.g., Barnard et al. (*J. Pathol.* 1987 Aug; **152** (4): 287-295).
[2] See, e.g., Sano et al. (*Am. J. Pathol.* 1998 Dec; **153** (6): 1741-1748) (of record; cited by Applicant).
[3] See, e.g., Brown et al. (*Br. J. Cancer.* 1988 Feb; **57** (2): 178-81).

detect $p16^{INK4a}$ and Ki67 in biological samples because it would not have been necessary to acquire and use secondary antibodies and indirect labeling reagents. There were at the time many different "labels" that might have been used, including, for example, fluorescent labels having different emission spectra, which would permit simultaneous measurements to be made where more than one fluorescently labeled antibody is used at the same time to stain cells expressing one or both antigens.

Notably, claim 35 has been amended to recite a limitation that the kit comprises primary and secondary antibodies that are obtained from different animals, and Martin et al. teaches primary antibodies that were obtained from mice and secondary antibodies that were obtained from goats; see, e.g., page 1574, column 2. Martin et al. teaches the primary antibodies are labeled with secondary antibodies that are labeled with different enzymes that produced distinguishable detectable signals that permit double labeling of cells and simultaneous analysis of both $p16^{INK4a}$ and Ki67; see, e.g., page 1574, column 2.

Though Martin et al. does not expressly teach that the primary antibodies used were obtained from different animals, since both antibodies were obtained from mice, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have manufactured the kit using a first primary antibody obtained from one animal (e.g., a mouse) and a second primary antibody obtained from another animal (e.g., a rat) simply because it was so very routine and conventional at the time to use antibodies obtained from different animals (e.g., mice, rats, rabbits, sheep, and goats) at the time. Indeed, it would have been so obvious to do so that it is submitted that this difference need not be explicitly taught or suggested by the reference itself, as the claimed invention would have been an obvious variant of that which is expressly described by the reference given only the knowledge generally available to one of ordinary skill in the art.

Moreover, it is submitted that careful consideration of the record will show that there most definitely was that requisite "something" in the prior art as a whole to suggest the desirability, and thus the obviousness, of combining the teachings of the cited reference and otherwise only the knowledge generally available to one of ordinary skill

in the art to thereby make the claimed invention. See *Continental Can Company USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1271, 20 USPQ2d 1746, 1751 (Fed. Cir. 1991).

With regard to claim 49, although Martin et al. does not expressly teach that secondary antibody is a rabbit antibody, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have manufactured the kit using a secondary antibody obtained from a rabbit simply because it was so very routine and conventional at the time to use rabbit anti-mouse antibodies at the time to perform such indirect analyses. Moreover, the use of a rabbit antibody, as opposed to a goat antibody, as a secondary antibody is an obvious variation, given only the knowledge generally available to one of ordinary skill in the art, and need not be explicitly taught or suggested by the reference itself. As explained, one of ordinary skill in the art at the time the invention was made would have been motivated to produce the kit because such kits had become widely used in such research, having established utility in such expression studies, for example, and providing ease of use and convenience, as well as greater uniformity and control.

It is submitted that this matter represents a clear, "text-book" case of obviousness under 35 U.S.C. § 103.

The claimed kit comprises known compounds, which can be used together in a known way to achieve predictable results.

It is no surprise that one might use a mouse antibody that binds $p16^{INK4a}$ and then a rat antibody, for example, instead of another mouse antibody that binds the Ki67/Ki-S5; similarly it is of no surprise that one might use an anti-mouse goat antibody as a secondary antibody to detect the mouse antibody that binds $p16^{INK4a}$, but an anti-rat hamster antibody as a secondary antibody to detect a rat antibody that binds Ki67/Ki-S5.

Applicant is therefore reminded that "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results," *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 [82 USPQ2d 1385, 1389] (2007).

Thus, the case of obviousness meets the appropriate standard for obviousness under 35 U.S.C. § 103, since the whole of the claimed process is taught or suggested by the prior art, where there is some teaching, suggestion, incentive, or inference found in the applied references, or in knowledge generally available to the artisan of ordinary skill in the art, which would have motivated the artisan to practice the claimed invention with a reasonable expectation of success.

8. Claims 35, 39, 42, 43, 48, and 49 are rejected under 35 U.S.C. 103(a), as being unpatentable over Martin et al. (*Am. J. Pathol.* 2000 May; **156** (5): 1573-1579) (of record) in view of Sano et al. (*Am. J. Pathol.* 1998 Dec; **153** (6): 1741-1748) (of record; cited by Applicant) and Brown et al. (*Br. J. Cancer.* 1988 Feb; **57** (2): 178-81).

Claims 35, 39, 42, 43, 48, and 49 are drawn to a kit comprising a first primary antibody that binds to $p16^{INK4a}$ polypeptide, a second primary antibody that binds to Ki67 polypeptide, and a sample of cervical cells expressing $p16^{INK4a}$ and Ki67, which could be used as a positive control.

Martin et al. teaches and/or suggests that which is set forth in the above rejection of the claims.

If, arguably, the disclosure by Martin et al. alone would not have rendered the claimed invention obvious since it fails to expressly describe a *cervical* cell, per se, which expresses both $p16^{INK4a}$ and Ki67, which may be used as a positive control, and which could be included in a kit as a positive control, then, it is submitted that it would have been *prima facie* obvious to utilize a cervical cell as a positive control because according to Sano et al. and Brown et al. cervical cells express both proteins. Any cell, including a cervical cell that expresses $p16^{INK4a}$ and Ki67 could be suitably used as a positive control; and this fact would have been immediately apparent to the artisan of ordinary skill in the art at the time the application was filed.

Conclusion

9. No claim is allowed.

10. As previously noted in the Office action mailed August 1, 2008, the prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Both Dai et al. (*Gastroenterol.* 2000 Oct; **119** (4): 929-942) (of record) and Emig et al. (*Br. J. Cancer.* 1998 Dec; **78** (12): 1661-1668) (of record) teaches an analysis of the levels of p16 and Ki67 in the same samples.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

slr
June 8, 2009